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FOCUS ON INFLUENZA

With this issue, we begin a two-issue series focusing on pandemic influenza. In this issue, see Influenza: Lessons for the clinic from 1918, below, and Cytokines and Herbal Therapeutics in Influenza on page 5. In our next issue, we will feature three clinical articles: Influenza prevention, Therapeutics for acute febrile illness, and Therapeutics for the acute cough.

Influenza: Lesson for the clinic from 1918

by Paul Bergner

Abstract: Avian influenza and the potential threat of a major influenza pandemic have been among the top news stories over the past year. Public health concern is high because of the high human mortality rate associated with bird flu and fears of the potential for emerging strains to spread from human to human. Coupled with the news stories are accounts of the deadly 1918 influenza pandemic. The "superbug" theory of pandemic influenza generally attributes all excess mortality to the strength of the pathogen and ignores all other factors involved in host resistance. This theoretical stance does not withstand close critical examination, particularly in light of what is historically known about the 1918 pandemic. Factors such as urbanization, micronutrient malnutrition, poor diet, vitamin D deficiency, and host-weakening iatrogenic disease may have contributed significantly to mortality in the 1918 pandemic, and these factors may have been as important as the pathogenic potential of the virus. An examination of these factors from 1918 leads to recommendations for prevention or treatment during future pandemics.

By their very nature, viruses constantly mutate and evolve, partly in response to host resistance in general, but also in response to the specific host carrier. Influenza viruses mutate and evolve in human, bird, and pig hosts, and spread between these hosts in agricultural areas. Viral strains may evolve characteristics that make them more or less lethal to humans, with more or less facility of transmission, and mortality may vary somewhat from season to season. The contemporary concern of public health authorities is that a strain with unusual lethality could develop, killing millions of people worldwide and causing widespread social and economic disruption through secondary effects. Of special concern is the current epidemic of Avian Influenza H5N1, which primarily infects birds. Bird-to-human infection has a high mortality rate – estimated at about 50% of those hospitalized with the disease (Wong and Yuen). Actually lethality may be much less, because asymptomatic, subclinical, or mild illness is unlikely to come to the attention of authorities, and only those most severely affected are hospitalized. Whether the virus will mutate to allow human-to-human transmission – and whether such a mutation will retain the lethality of the current bird virus – is a matter of serious concern.

Typical seasonal influenza infections are one of the leading causes of death in the United States. Of the 30,000 to 70,000 influenza-related deaths per year, most involve the elderly or those with compromised immune systems. In North America, mortality of these typical viruses is 1/10,000; in the 1918 flu pandemic, mortality was 2/1000, about 20 times normal. Mortality in 1918 among Native American populations was extremely high. Up to 80% died in some Eskimo villages, and 10% of the entire population died in the state of Chiapas, Mexico. This phenomenon among Native Americans may be similar to the plagues of Western diseases that decimated native peoples around the world following first European contact, with a large percentage of the native population lacking innate immunity to influenza and other Eurasian diseases (Barry; Killingray; Newman). No such lethal epidemic of influenza had been recorded previously, or since, and this has become the reference point for most discussions of unusually deadly organisms.

HOST FACTORS

An examination of the social and public health conditions of the Western urbanized societies in the early twentieth century offers alternate explanations for the lethality of the 1918 epidemic. Urban social and public health conditions may have contributed significantly to

the epidemic, and these factors tend to modify the preeminence of pathogen strength as the sole cause of excess mortality. It was established during the 1918 epidemic that a large percentage of the population either did not get infected, or experienced only subclinical symptoms. In several trials at the time, subjects were unable to become infected even though experimentally exposed. In these cases, their host resistance was able to withstand exposure or generate immunity without producing symptoms. In an experiment with prisoners in a U.S. Navy brig in Boston, researchers were unable to infect any of 100 "volunteers," despite exposing them to infected individuals and to their mucous secretions (Rosenau). None had shown any previous signs of having contracted the virus between the outbreak of the epidemic and the experiment. The following account summarizes the procedures used:

> *"Then we proceeded to transfer the virus obtained from cases of the disease; that is, we collected the material and mucous secretions of the mouth and nose and bronchi from cases of the disease and transferred this to our volunteers. We always obtained the material in the following way: The patients with fever, in bed, have a large, shallow, traylike arrangement before him or her, and we washed out one nostril with some sterile salt solution, using perhaps 5 c.c., which is allowed to run into this tray; and that nostril is blown vigorously into the tray. That is repeated with the other nostril. The patient then gargles the solution. Next we obtain some bronchial mucous through coughing, and then we swab the mucous surface of each nares and also the mucous membranes of the throat."*

Two similar experiments in other localities had identical results (Kolata). These results are inexplicable given the high mortality rates of the virus in other settings. The only possible explanation is host resistance.

HOST FACTORS IN THE 1918 PANDEMIC

Any infectious disease is the result of interaction between the infectious agent and the host resistance to it. Some agents are weak enough that anyone with strong host resistance will not acquire the disease; others may be so powerful that only a very few will be able to resist infection and disease. Most influenza strains are intermediate in strength, and some individuals with strong host resistance can avoid infectious symptoms and develop immunity without acquiring symptomatic illness. Those with moderate host resistance may acquire the illness without serious consequences, while those with weakened immunity are most likely to have the most severe, and potentially lethal, symptoms.

This equation of balance between host immunity and pathogenicity is almost universally ignored in discussions of potent new strains of influenza. From a public health perspective, this balance should be the primary topic of discussion because measures to increase resistance are easier and cheaper to implement on a mass scale than the measures required to develop and administer vaccines and pharmaceutical drugs. Compared to the costs and logistical problems involved in major medical campaigns, measures such as public education, improved nutrition, and environmental modifications are a cost-effective way to increase host resistance on a large scale. Even if vaccines become more effective than those available at present, or if drugs are developed that do not ultimately promote drug-resistance, these other measures to improve host resistance to influenza will continue to be effective on an individual, practice-level, or broad social scale. They may also increase the effectiveness of vaccines and antiviral drugs. See the accompanying article Influenza Prevention.

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An examination of the social conditions in industrialized countries in 1918 may reveal that specific factors profoundly influenced host resistance, especially in the younger generation. The 1918 epidemic came after several decades of urbanization in North America, involving a major population shift from farm to city, and to the conditions of labor and diet in the city. During this same period, sugar and white flour became available as staple foods rather than specialty foods, and they became a major portion of the diet. Flour used during this period did not contain the vitamins in whole grains that are lost during processing, and it was many decades before the advent of fortified processed foods. The resulting deficiencies included reduced intake of many immune-supporting nutrients such as zinc, vitamin A, vitamin C, vitamin E, selenium, iron, and essential fatty acids (See accompanying article Influenza Prevention). As a result, as the population of North America increasingly relied on processed grains, the general health, constitution, and immunity of the population weakened over time. By 1900, white sugar consumption had grown to exceed 100 lbs of sugar per capita in the United States – or 4 to 5 ounces per day – with most of the consumption occurring in urban areas. Sucrose or its derivative glucose are known to be immuno-suppressive in the amounts consumed by urban dwellers in 1918. In one study, 3 ounces of sucrose at one sitting reduced the ability of phagocytes to engulf bacteria and other invaders by

about 40%. The effect started within 30 minutes and lasted more than 5 hours (Sanchez et al 1973; Ringsdorf et al 1976). Another trial showed that only 2 ounces of glucose suppressed the activity of B- and T-lymphocytes (Bernstein 1977).

While researchers have proposed that the young died in greater numbers than the old during the 1918 epidemic because they had healthier immune systems and could mount a more powerful self-destructive cytokine storm than older patients (See the accompanying Cytokines and Herbal Therapeutics in Influenza), observers at the time noted that the young were in fact weaker and more sickly than their elders during the decade of the epidemic. In the 1916, dentist and nutritional anthropologist Weston Price was stricken by the phenomenon of sickly, urban youth in Cleveland, Ohio – particularly those from families with robust farm-raised parents and grandparents. In response to this phenomena, he pursued worldwide studies linking modern dietary changes to physical degeneration, with documentation by photograph in his classic *Nutrition and Physical Degeneration* (Price). The photographs showing the deterioration of the health of children relative to their parents or to others following a traditional rather than modern diet. One photograph shows an older Scottish brother, eating a traditional diet, with robust health, while the younger brother, freely eating pastries and sugar, with his bone structure and teeth deteriorated. The same degeneration of the constitution was noted by nature cure physician Henry Lindlahr in Chicago. In 1913, Lindlahr described a generation of healthy grandparents, "anemic" parents, and "sickly children subjected to the full horrors of urban life". (Lindlahr). Child labor also peaked in the U.S. during the first decades of the twentieth century (CLPEP) and many children were not only malnourished but were also subjected to dawn-to-dusk working conditions. It is possible that the pandemic struck this younger generation like a forest fire among insect-infested trees.

VITAMIN D

The new urban labor conditions in 1916 North America kept factory workers, including children, indoors and out of the sun for most or all of the day – with an epidemic of Vitamin D deficiency as the result. The role of vitamin D in defense against influenza cannot be overestimated (for a full review see the Cannell article in the references). The seasonality of influenza correlates precisely to the darkest seasons of the year in both the Northern and Southern temperate zones and during cloudy monsoon seasons in the tropics. One role of Vitamin D is to promote immuno-competent peptides in the immune cells of the respiratory tract; another is to blunt the severity of inflammation during infection. Together these two functions are the perfect combination to prevent influenza infection or to modify excessive inflammation from cytokine effects and render the infection less lethal. In intervention trials, vitamin D given as cod liver oil has shown much better results for prevention of respiratory infection during flu season, or reduction of severity of symptoms, than influenza immunizations (Cannell). Cod liver also contains vitamin A and essential fatty acids, both may benefit host resistance. In one cited study, the vitamin D dose for children equivalent to 4,000 IU in an adult completely prevented all respiratory infection over a winter in a group of children who had experienced three or more infections the previous year.

IATROGENIC INJURY

Many recorded features of the 1918 flu do not match the natural course of the disease, but are common side effects of methods used to treat the infection at the time. Aspirin was a new drug at the time, as were several medications similar to acetaminophen with poorly defined toxicity. Two recorded sample prescriptions for influenza during the epidemic follow (Anonymous):

Prescription 1

Aspirin	1300 mg
Phenacetine	650 mg
Salol	1300 mg

Prescription 2

Aspirin	1300 mg
Acatanilid	260 mg

Phenacetine and N-phenylacetamide are in the drug class with acetaminophen. Salol yields about 60% salicylic acid. These combinations of aspirin and non-steroidal anti-inflammatory drugs (NSAID) are in line with what might be recommended today for febrile illness, but similar doses have been found to be immuno-suppressive in viral respiratory illnesses, including influenza. In 1975, a pair of double-blind trials administered either aspirin or placebo to volunteers experimentally infected with rhinovirus, the most common virus to cause the common cold. Aspirin reduced the symptoms somewhat, but caused a "highly significant" increase in virus production. The authors stated that such treatment could worsen viral illness and contribute to its spread (Stanley et al.). In 1990, other researchers tested the effects of aspirin and acetaminophen on experimental rhinovirus infection. The use of either drug suppressed antibody response to the virus and prolonged the time that infected cells produced new virus (Graham et al.). In 2000, researchers tested the effects of antipyretic therapy with aspirin or acetaminophen on experimentally produced influenza A virus. The authors noted a "striking" prolongation of influenza infection in the patients who

took either aspirin or acetaminophen (Plaisance et al.). It would seem that the routine administration of these drugs during the epidemic weakened resistance to the illness, prolonged the illness, and may have made it more infectious. In addition, the combination of aspirin and NSAID may have made matters worse. Today standard references warn against giving aspirin in doses higher than 325 mg if accompanied by an NSAID. Note that treatment of fever with NSAID is standard treatment today in H5N1 infection despite the above research, and this treatment approach may contribute to the reported lethality of the disease. Treatment of advanced complications of H5N1 with immuno-suppressive corticosteroids has also been standard until recent recommendations against it (WHO).

Besides weakening host immunity, aspirin may have also contributed to the distorted presentation of the 1918 pandemic. So many patients demonstrated hemorrhagic symptoms, that it is now often included as a symptom of that pandemic, even though it is not part of the normal course of influenza (Barry). Aspirin can cause such symptoms, sometimes even at low doses. One contemporary trial found that 200 mg of aspirin per day taken chronically causes major bleeding events in about 4% of patients (Peters et al.) Aspirin had only been available to the medical profession and the public for about 20 years before the epidemic, and its toxicity was not well known. In 1918, there are reports of doctors giving as much aspirin as a patient could tolerate, and doses up to 6.5 grams for several days in a row (Winston). Aspirin and other medications were available over the counter in an era when safety warnings were absent and prescriptions were not required for any medications. Other side effects of aspirin overdose also overlap with symptoms of epidemic influenza, including respiratory collapse and shock. High doses of aspirin may also explain some of the mortality in the younger generation through the effects of Reyes syndrome. Reyes syndrome is associated with multiple organ failure in individuals under the age of eighteen with viral illness who take aspirin.

Besides weakening host immunity, aspirin and other drugs may have also distorted the clinical presentation of the 1918

The other two drugs in common prescriptions, Acetanilid and Phenacetine, are no longer sold because safer alternatives are available. Phenacetine has a depressant action on the heart, where it can disrupt electrolyte activity. Its use has been discontinued due to potential carcinogenicity with chronic administration. Acetanilid (N-phenylacetamide) can cause a rapid and sudden drop of fever, which may be also accompanied by cardiovascular collapse (Osol and Farrar). In acute poisoning, acetanilid causes cyanosis with subsequent prostration and collapse. Traditionally, and at the time of the 1918 epidemic, acetanilid was given with caffeine, which increases its toxicity (Osol and Farrar). Notably, cyanosis and sudden circulatory collapse were two symptoms often noted in the 1918 flu epidemic (Barry). We wonder if these and some of the unusual symptoms reported for the 1918 influenza were not, in fact, side effects of the medications routinely given. For example, an account from a military hospital in Massachusetts indicates that the patients

".... start with what appears to be an ordinary attack of . . . influenza, and when brought to the hospital they very rapidly develop the most viscous type of pneumonia that has ever been seen. Two hours after admission they have the mahogany spots over the cheek bones, and a few hours later you can begin to see the cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the colored men from the white. It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate. It is horrible. One can stand it to see one, two or twenty men die, but to see these poor devils dropping like flies sort of gets on your nerves. We have been averaging about 100 deaths per day, and still keeping it up. " (Leavitt)

The 1918 epidemic normally had a mortality rate of about 3%; it appears that whatever treatment was given in the above hospital was killing the patients because cyanotic symptoms are not part of the natural course of influenza. Because all of these medications were available over the counter in 1918, some individuals who self-medicated likely took overdoses of the drugs, possibly before entering the hospital. It seems likely that then, as now, some individuals overdose when self-medicating with aspirin — aspirin overdoses are the fourth most common drug overdose in conventional emergency care. It would take only a few percent of patients over-medicating with these drugs to produce much of the excess mortality noted in the epidemic.

VACCINES

Further iatrogenic injury may have contributed to excess mortality in the 1918 epidemic. Vaccines and antitoxins to various non-influenza diseases were routinely given to patients with acute influenza. Typhoid vaccine was a common prescription, and "others poured every known vaccine into patients in the hopes that they would somehow boost immunity" (Barry). While neurological complications of vaccines are common, the neurological complications of influenza patients in 1918 were attributed entirely to the virus.

DIGITALIS

Hospitalized influenza patients were administered digitalis as a matter of course; this was a standard treatment at Johns Hopkins. In 1918, the drug was administered as powdered leaf of the digitalis plant. Accurate dosing of dried plant material is difficult, as the active constituents in the plant degrade rapidly in powdered material (Osol and Farrar). In addition, dosing is complicated by the fact that the toxic dose is very close to the therapeutic dose. In standard practice, the herb dose was administered until its strengthening effects on the heart and pulse were noted, and then the dose was increased again until nausea appeared. Nausea and vomiting are the first signs of toxicity. Headache, fatigue, malaise, and drowsiness are the next signs to appear, and all are indicators for a reduction of the dose. Because these signs of toxicity overlap almost completely with typical signs of acute influenza, the possibility of overdosing the patient and inducing heart arrhythmia and cardiac collapse was great.

OPIATES

Other drugs routinely given were heroin hydrochloride, codeine sulphate, cocaine hydrochloridum, opium, morphine sulphate, elixer terpin hydrate (a concoction of terpentine, alcohol, and nitric acid), paregoric elixer (made with powdered opium, benzoic acid, camphor, oil of anise, and glycerin diluted alcohol), and morphine

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Acute and chronic opioid administration is known to have inhibitory effects on humoral and cellular immune responses including antibody production, natural killer cell activity, cytokine expression, and phagocytic activity. Opiate receptors modify immunity by action on the central nervous system, the autonomic system, and directly on immune cells (Vallejo et al; Molina). Opiates also specifically depress the numbers of circulating natural-killer cells, which are responsible for attacking virally-infected host cells (Weed et al.). Opiates are suspected to increase susceptibility and to decrease resistance to the spread of viruses such as HIV and the hepatitis-C Virus Cabral; Zhang et al). Opiates also increase susceptibility to bacterial infections in burn patients (Schwacha et al.).

LESSONS FOR THE CLINIC

- Increase host resistance with diet and lifestyle approaching flu season.
- Take 4,000 to 10,000 IU of vitamin D during winter season.
- Don't suppress fever or immunity with aspirin, NSAID, or other medications.

Cytokines and Herbal Therapeutics in Influenza

By Paul Bergner

One theory for the higher mortality of Avian Flu H5N1and of the 1918 influenza strain is that an excessive immune response contributes to the pathology and lethality of the disease (Cheung et al). Immune cells pour out inflammatory cytokines in an attempt to destroy invading pathogens, and this may occur more or less intensely depending on the influenza strain. According to this "cytokine storm" theory, lymphocytes and macrophages may produce a sustained and massive cytokine response in response to a "superbug," leading to severe systemic inflammation and destruction of tissues, especially in the lungs (Hseih et al). According to the theory, an individual with a strong immune system would be more likely to die than an individual with a weak immune response. This theory has been put forth as an explanation for why the 1918 epidemic struck young patients with more virulence than the old, reversing the typical epidemiology of the disease (Loo and Gale). This theory also raises questions about the wisdom of using herbal medicines that stimulate immunity during influenza infection.

The cytokine storm theory for the lethality of some influenza strains is by no means settled science. Alternative explanations for the elevated lethality in flu "superbugs" have been put forth in the scientific literature. Although more than one phenomenon may contribute to overall mortality at the same time, the ability of the H5N1 avian influenza virus to escape the respiratory epithelium and to produce a widely-disseminated systemic infection may be more important to pathogenesis of the disease than exaggerated cytokine response. Influenza infection is normally restricted to the upper respiratory tract.

Another alternate theory suggest that vitamin D status may be a critical determinant of total cytokine effects, and not only determines susceptibility to influenza infection, but also the severity of symptoms (Cannell et al). The Cannell article is part of a significant body of recent scientific literature establishing widespread vitamin D deficiency as a major root pathology in many contemporary diseases. One of the chief physiological roles of vitamin D, an immuno-modulator steroid hormone, is to put a brake on inflammatory cytokine responses, and thus the deficiency may play a role is pathological cytokine excess. Note that in 1918, the world was entering into a period of rapid urbanization, with new factory working conditions which often kept the individual out of direct sunlight 6 days a week – conditions which pro-

mote profound vitamin D deficiency. Typical seasonal influenza is closely and inversely related to average vitamin D status of humans, peaking throughout the world at local times when vitamin D status is at its lowest.

CYTOKINES AND SUDDEN DEATH

A characteristic of the 1918 influenza was the sudden death of some of its victims. Anecdotal accounts tell of four men sitting down to play a card game in the evening, with only one of them left alive in the morning. Another tells of several individuals dying on a streetcar within several blocks, including the conductor. From the natural course of influenza infection, it is unlikely that these individuals died at first onset of the illness. More likely is that they left their sick beds too soon. The typical course of influenza infection, as measured by the presence of cytokines, is 1 full week. Different cytokines surge or peak at different times over this period, but peaks may occur as late as Day 6. The initial fever of influenza often recedes between Days 2 and 4 as the levels of one set of cytokines decreases. On Days 4 to 6, as patients may begin to feel some relief from symptoms, cytokines associated with lower respiratory infection may surge (Hayden et al). The symptoms are less dramatic, but the complications and lethality of a lower respiratory infection and inflammation may nevertheless be quite severe. It is common in contemporary times for patients to leave their beds and return to work when the fever of influenza first subsides. In one recent year, the author had six patients with influenza, all of whom felt better by Day 3. They were cautioned to rest for a full seven days, but two of them went back to work on Day 4 of their infections. Both relapsed with viral pneumonia and were hospitalized on Day 6 of the infection. Similar behaviors in the 1918 epidemic may have led to the high incidence of sudden death as those who left their beds too early died in public of lower respiratory infection and inflammation.

Doctors at John's Hopkins medical school conducted a retrospective analysis of which patients did better or worse with various medical treatments in the 1918 pandemic. The analysis found only that those who "went to bed the earliest, stayed there the longest, and had the best nursing care survived the best" (Barry).

HERBS AND CYTOKINES

Physician-level treatment of influenza with herbal medicines has been recorded at least since the 18th century in North America (Lloyd and Lloyd). Several of the most common herbs used, *Sambucus nigra, Eupatorium perfoliatum,* and *Echinacea spp.*, have been shown through scientific investigation to enhance host immunity (Brush et al; Zakay-Rones et al; Wagner et al; Wagner and Jurcic). A critical question in light of the cytokine theory in the pathology of influenza is whether an herbal agent that enhances host resistance may also increase pathological expressions of cytokines. Many herbal medicines with reputation as immuno-stimulant actually have immuno-modulating effects, enhancing some inflammatory cytokines while moderating their effects by stimulating secretion of inhibitory cytokines along with them.

ELDERBERRY

Sambucus nigra, elderberry berries or flowers, are used in traditional herbalism to treat respiratory infections, including influenza. Clinical trials over the last decade have demonstrated a powerful effect of an elderberry extract syrup on the course of influenza (Zakay-Rones et al. 1995, 2004). The extract has also been shown to inhibit influenza virus replication in ten strains of the virus in vitro (Zakay-Rones 1995). Notably, elderberry extracts have been shown to enhance both inflammatory and anti-inflammatory cytokines in human cells in lab experiments (Barak et al). In one lab study, an extract of the flowers inhibited all pro-inflammatory cytokines measured (Harokopakis) and in another showed at least partial inhibition of inflammatory cytokines (Yesilada et al).

ECHINACEA AND BONESET

Echinacea species, used a hundred years ago in the treatment of influenza, and remaining a common treatment today may enhance immunity and also have a moderating effect on excessive inflammation (Sharma et al.; Randolph et al., Brush et al.; Zwickey et al.) One trial of the use of a combination of Echinacea and *Eupatorium perfoliatum* found no net inflammatory effect produced by cytokines in humans at the dose tested (Elsasser-Beile et al.) Eupatorium has been one of the frequently used herbs in the treatment of influenza in North American history (Lloyd and Lloyd).

In the absence of specific evidence that herbs traditionally used in the treatment of influenza aggravate the condition by overstimulating cytokines, there appears to be no reason to avoid their use for this speculative reason.

LESSONS FOR THE CLINIC

- Promote healthy vitamin D levels in patients as a preventive in the face of an approaching pandemic.
- Consider megadoses of vitamin D acutely at exposure or onset of symptoms in patients whose status is likely to be low.
- Treat acute infections with herbs according to historical usages, unless specific evidence emerges that they may exacerbate the symptoms or pathology of a hew pandemic influenza strain.

INFLUENZA REFERENCES

Anonymous. The story: Oshkosh in 1918. http://www.uwosh.edu/archives/flu/story1.htm

Barak V, Birkenfeld S, Halperin T, Kalickman I. The effect of herbal remedies on the production of human inflammatory and anti-inflammatory cytokines. *Isr Med Assoc J.* 2002 Nov;4(11 Suppl):919-22.

Barry, JM. *The Great Influenza.* New York: Viking, 2004.

Bernstein, J. Alpert, S. Nauss, K. and Suskind, R. Depression of lympocyte transformation following glucose ingestion. *Am J Clin Nutr* 1977;30:613

Brush J, Mendenhall E, Guggenheim A, Chan T, et al. The Effect of Echinacea purpurea, Astragalus membranaceus and Glycyrrhiza glabra on CD69 Expression and Immune Cell Activation in Humans. *Phytother. Res*. 20, 687–695 (2006)

Cabral GA. Drugs of abuse, immune modulation, and AIDS. *J Neuroimmune Pharmacol.* 2006 Sep;1(3):280-95. Epub 2006 Jun 28.

Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, et al. Epidemic influenza and vitamin D. *Epidemiol Infect*. 2006 Dec; 134(6): 1129-40.

Chan MC, Cheung CY, Chui WH, Tsao SW, et al. Proinflammatory cytokine responses induced by influenza A (H5N1) viruses in primary human alveolar and bronchial epithelial cells. *Respir Res.* 2005 Nov 11;6:135.

Cheung CY, Poon LL, Lau AS, Luk W, et al. Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: a mechanism for the unusual severity of human disease? *Lancet.* 2002 Dec 7;360(9348): 1801-2.

CLPEP Child Labor Public Education Project. http://www.continuetolearn.uiowa.edu/laaborctr/child_labor/about/us_history.html

Elsasser-Beile U, Willenbacher W, Bartsch HH, Gallati H, Schulte Monting J, von Kleist S. Cytokine production in leukocyte cultures during therapy with Echinacea extract. *J Clin Lab Anal.* 1996;10(6):441-5.

Graham NM, Burrell CJ, Douglas RM, Debelle P, Davies L.Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. *J Infect Dis.* 1990 Dec; 162(6): 1277-82.

Harokopakis E, Albzreh MH, Haase EM, Scannapieco FA, Hajishengallis G. Inhibition of proinflammatory activities of major periodontal pathogens by aqueous extracts from elder flower (Sambucus nigra). *J Periodontol.* 2006 Feb;77(2):271-9.

Hathcock J, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Am J Clin Nutr* 2007;85:6–18.

Hayden FG, Fritz R, Lobo MC, Alvord W, Strober W, Straus SE. Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. *J Clin Invest.* 1998 Feb 1;101(3):643-9.

Hsieh YC, Wu TZ, Liu DP, Shao PL, Chang LY, et al. Influenza pandemics: past, present and future. *J Formos Med Assoc.* 2006 Jan;105(1):1-6.

James J Nutrition and HIV infection:Experience in Zimbabwe— interview with Lynde Francis. *The Body.* 11-17-2000 http://www.thebody.com/content/world/art32034.html [accessed 12/6/2007]

Killingray D. The influenza pandemic of 1918-1919 in the British Caribbean. *Soc Hist Med.* 1994 Apr;7(1):59-87.

Kolata G. Flu: *The Story fo the Great Influenza Pandemic of 1918 and the Search for the Virus That Caused It.* New York: Farrar, Strous and Giroux, 1999.

Leavitt M. Massachusetts State Summit History Supplement http://www.pandemicflu.gov/general/greatpandemic2.html #massachusetts [08-13-2007]

Lindlahr H. *Nature Cure.* IndyPublish (reprint October 12, 2006)

Lloyd JU and Lloyd CG. *A Treatise on Eupatorium perfoliatum.* Drug Treatise Number XXXI. Lloyd Brothers Pharmaceutical Company. 1918.

Loo Y-M, Gale M. Influenza:Fatal immunity and the 1918 virus. *Nature* 445, 267 - 268

Molina PE. Opioids and opiates: analgesia with cardiovascular, haemodynamic and immune implications in critical illness. *J Intern Med.* 2006 Feb;259(2):138-54.

Newman MT. Aboriginal new world epidemiolgy and medical care, and the impact of Old World disease imports. *Am J Phys Anthropol.* 1976 Nov;45(3 pt. 2):667-72.

Osol A., and Farrar G.E. *The Dispensatory of the United States of America.* The 24th Edition. Philadelphia: J.B. Lippencott Company, 1947

Peters JG, Mehta SR, Fox KAA, Zhao F, Lewis BS, Kopecky L., et al. Effects of Aspirin Dose When Used Alone or in Combination With Clopidogrel in Patients With Acute Coronary Syndromes: Observations From the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Study. *Circulation.* 2003; 108; 1682-1687

Plaisance KI, Kudaravalli S, Wasserman SS, Levine MM, Mackowiak PA.Effect of antipyretic therapy on the duration of illness in experimental influenza A, Shigella sonnei, and Rickettsia rickettsii infections. *Pharmacotherapy.* 2000 Dec;20(12):1417-22.

Price W. *Nutrition and Physical Degeneration.* Price-Pottenger Nutrition Foundation; Sixth edition (reprint 2004).

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Randolph RK, Gellenbeck K, Stonebrook K, Brovelli E, Qian Y, Bankaitis-Davis D, Cheronis J. Regulation of human immune gene expression as influenced by a commercial blended Echinacea product: preliminary studies. *Exp Biol Med* (Maywood). 2003 Oct;228(9):1051-6.

Ravaglia G, Forti P, Maioli F, Bastagli L, Facchini A, et al Effect of micronutrient status on natural killer cell immune function in healthy free-living subjects aged 90 y *American Journal of Clinical Nutrition,* Vol. 71, No. 2, 590-598, February 2000

Ringsdorf, W., Cheraskin, E., and Ramsay, R. Sucrose, neutrophilic phagocytosis and resistance to disease. *Dent Surv* 1976;52:46-48

Rosenau, MJ. Experiments to determine mode of spread of influenza. *JAMA.* 1919;73:311-313.

Sanchez, A., Reeser, J., Lau, H. et al. Role of sugars in human neutrophilic phagocytosis. *Am J Clin Nutr* 1973;26: 1180-1184

SAT (Southern African AIDS Training Programme). *Counselling guidelines on survival skills for people living with HIV.* Canadian International Development Agency. July 2001

Schoop R, Klein P, Suter A, Johnston SL. Echinacea in the prevention of induced rhinovirus colds: a meta-analysis. *Clin Ther*. 2006 Feb;28(2):174-83.

Schwacha MG, McGwin G Jr, Hutchinson CB, Cross JM, Maclennan PA, Rue LW 3rd. The contribution of opiate analgesics to the development of infectious complications in burn patients. *Am J Surg.* 2006 Jul;192(1):82-6.

Semba RD, Ndugwa C, Perry RT, Clark TD, Jackson JB, Melikian G, Tielsch J, Mmiro F.Effect of periodic vitamin A supplementation on mortality and morbidity of human immunodeficiency virus-infected children in Uganda: A controlled clinical trial. *Nutrition.* 2005 Jan;21(1):25-31.

Sharma M, Arnason JT, Burt A, Hudson JB. Echinacea extracts modulate the pattern of chemokine and cytokine secretion in rhinovirus-infected and uninfected epithelial cells. *Phytother Res.* 2006 Feb;20(2):147-52

Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy.*Lancet Infect Dis* 2007; 7:658-666

Stanley ED, Jackson GG, Panusarn C, Rubenis M, Dirda V. Increased virus shedding with aspirin treatment of rhinovirus infection. *JAMA.* 1975 Mar 24;231(12):1248-51.

Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. *Am J Ther.* 2004 Sep-Oct;11(5):354-65.

Wagner H, Jurcic K. Immunologic studies of plant combination preparations. In-vitro and in-vivo studies on the stimulation of phagocytosis. *Arzneimittelforschung.* 1991 Oct;41(10):1072-6.

Wagner H, Proksch A, Riess-Maurer I, Vollmar A, Odenthal S, Stuppner H, Jurcic K, Le Turdu M, Fang JN Immunostimulating action of polysaccharides (heteroglycans) from higher plants. *Arzneimittelforschung.* 1985;35(7):1069-75.

Weed MR, Carruth LM, Adams RJ, Ator NA, Hienz RD.Morphine withdrawal dramatically reduces lymphocytes in morphine-dependent macaques. *J Neuroimmune Pharmacol*. 2006 Sep;1(3):250-9. Epub 2006 Jul 14.

World Health Organization. *Clinical management of human infection with avian influenza A (H5N1) virus.* Updated advice 15 August 2007 . http://www.who.int/csr/resources/publications/en/ index.html [accessed 9/15/2007]

Winston J. Influenza-1918: Homeopathy to the Rescue. *The New England Journal of Homeopathy.* 1998:7(1).

Wong S-SY, Yuen KY. Avian influenza virus infections in humans. *Chest.* 2006 Jan;129(1):156-68.

Ye°ilada E, Ustün O, Sezik E, Takaishi Y, Ono Y, Honda G. Inhibitory effects of Turkish folk remedies on inflammatory cytokines: interleukin-1alpha, interleukin-1beta and tumor necrosis factor alpha. *J Ethnopharmacol.* 1997 Sep;58(1):59-73.

Zakay-Rones Z, Thom E, Wollan T, Wadstein J. Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. *J Int Med Res.* 2004 Mar-Apr;32(2):132-40.

Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, Mumcuoglu. M.Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (Sambucus nigra L.) during an outbreak of influenza B Panama. *J Altern Complement Med.* 1995 Winter;1(4):361-9.

Zhang T, Li Y, Ho WZ. Drug abuse, innate immunity and hepatitis C virus. *Rev Med Virol.* 2006 Sep-Oct;16(5): 311-27.

Zwickey H, Brush J, Iacullo CM, Connelly E, Gregory WL, Soumyanath A, Buresh R. The effect of Echinacea purpurea, Astragalus membranaceus and Glycyrrhiza glabra on CD25 expression in humans: a pilot study. *Phytother Res.* 2007 Nov;21(11):1109-12.

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